MATRIA

November 26, 1999

Dockets Management Branch
Food and Drug Administration
5030 Fishers Lane, Room IO6 I
Rockville, Maryland 20850

Dear Sir/Madam:

Enclosed are Matria Healthcare, Inc., comments to the Food and Drug Administration (FDA) July 30, 1999, Federal Register announcement proposing that home uterine activity monitors be reclassified from Class III to Class II.

If further assistance is needed, do not hesitate to contact me.

Sincerely,

Timothy Y. Cowart

TC/ms

97P-0350

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Comments of Matria HealthCare
In Opposition to the
Proposed Reclassification of
Home Uterine Activity Monitors:

FDA Docket No. 97P-0350
64 Fed. Reg. 41435 (July 30, 1999)

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EXECUTIVE SUMMARY

Since 1986, home uterine activity monitors (HUAMs), when used for the early detection of preterm labor (PTL), have been classified as "Class III" under Section 5 13 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 360c. Thus, the Food and Drug Administration (FDA) has required HUAM manufacturers to demonstrate the effectiveness and safety of each device in a premarket approval application containing data from clinical efficacy studies.

FDA now proposes to reclassify HUAMs for PTL use as "Class II" and allow new entrants into the market with a showing of "substantial equivalence" to one of the three approved devices. Matria HealthCare manufactures the approved devices and submits these comments in order to explain why reclassification of HUAMs at this time would be unlawful, inappropriate, and inequitable.

First, the petition for reclassification must be denied because neither the petition nor FDA's notice of proposed reclassification demonstrates that there has been any "new information" since FDA's imposition of Class III PMA requirements on HUAMs for early detection of PTL. Second, Section 520(h)(4) of the FD&C Act prohibits FDA from using the safety and efficacy data from the studies contained in the three approved premarket approval applications -- whether or not reports of two of the studies have been published -- as the basis for reclassification of HUAMs for early detection of PTL. Third, FDA's reclassification decision is a complete reversal of agency policy lacking support in the administrative record. Fourth, the proposed special controls are inadequate and inappropriate to address the safety and effectiveness issues identified by FDA and by the Obstetrics and Gynecology Medical Devices Panel.

INTRODUCTION

Home uterine activity monitors (HUAMs) are intended to detect uterine contractions in a pregnant woman. Since 1986, these devices, when used for the early detection of preterm labor (PTL), have been classified as "Class III" under Section 513 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 360c. Accordingly, the Food and Drug Administration (FDA) has required HUAM manufacturers to demonstrate the effectiveness and safety of each device in a premarket approval application (PMA) containing data from clinical efficacy studies. In particular, each manufacturer has been required to demonstrate the individual contribution of its monitor to the early detection of PTL as evidenced by cervical dilation (cm) at the time of PTL diagnosis. In thirteen years, only three PMAs, out of seven submitted, have been approved for HUAMs.

FDA now proposes to reclassify HUAMs for PTL use as "Class II" and allow new entrants into the market with merely a showing of "substantial equivalence" to one of the three approved devices. Matria HealthCare, Inc. (Matria) manufactures the approved devices and submits these comments in order to explain why reclassification of HUAMs at this time would be unlawful, inappropriate, and inequitable. [1]

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1. Matria was formed in 1996 by a merger of Healthdyne and Tokos Medical Corporation (Tokos). Although comments on FDA's reclassification proposal were initially due October 28, 1999, FDA granted an extension to November 26, 1990 to file its comments. Letter from Linda Kahan, FDA to Timothy Y. Cowart, Matria (October 22, 1999)

II. BACKGROUND

A. Medical Background

1. Preterm Labor

Labor is the physiological process by which the uterus expels, or attempts to expel, the fetus and placenta at 20 weeks or more of gestation.* It has historically been diagnosed, and is still diagnosed, on the basis of such factors as a progressive increase in the frequency and intensity of uterine contractions, the progressive effacement (shortening) and dilation of the cervix, and the progressive descent of the fetus through the birth canal.[3] For instance, the American College of Obstetricians and Gynecologists (ACOG) defines the onset of labor as the establishment of regular uterine contractions together with the beginning of dilation of the cervix.[4] The normal gestational period is 38-42 weeks. Labor occurring at or near this time is described as "term" or "full term" labor. Labor occurring between 20 and 37 weeks of gestation is referred to as "preterm" labor. Preterm labor occurs in 7 to 10 percent of all births and accounts for more than 85 percent of all perinatal complications and death.[5]

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2. Cunningham GF: Williams Obstetrics, 20th Ed. Stanford, Connecticut, Appleton & Lange, 1997.

3. Friedman EA: Labor: Clinical Evaluation and management, 2nd Ed. New Tork, Appleton Century & Crofts, 1978.

4. American College of Obstetricians & Gynecologists. Preterm Labor. ACOG Technical Bulletin No. 206, June 1995.

5. Norwitz ER, The Control of Labor, Mew Eng. J. Med. 1999 Aug 26:660-666.

The risk factors for PTL include previous preterm delivery, multiple gestation, uterine anomalies, infection, smoking, and demographic variables such as younger or older maternal age, black race, low weight before pregnancy, and low socioeconomic status.[6] Reliance on these risk factors alone, however, will fail to identity more than 50 percent of the women who will ultimately have preterm delivery.[7]

Preterm labor does not always result in preterm delivery; medical intervention can prevent preterm delivery in some cases.[8] The most common method of intervention is oral or intravenous administration of a tocolytic agent, such as magnesium sulfate, ritodrine hydrochloride, terbutaline sulfate, indomethecin, or a calcium channel blocker like nifedipine.[9] All tocolytics are, however, associated with potential maternal and neonatal side effects. For example, calcium channel blockers may have an adverse effect on uteroplacental blood flow, and magnesium sulfate can cause pulmonary edema in the mother.[10] While magnesium sulfate is generally viewed as the

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6. Id.

7. Id.

8. Von der Pool BA, "Preterm Labor: Diagnosis and treatment," Am. Fam. Physician 1998 May 15; 57(10): 2457-64.

9. Norwitz, supra note.

10. Id.

safest tocolytic drug and is the most commonly used, ritodrine hydrochloride is the only drug approved by FDA for treatment of preterm labor and is available in intravenous form for use in the hospital. Non-drug methods of intervention, such as bed rest and hydration, are also ordered but are less effective.

Tocolytic intervention is more effective if it occurs soon after preterm labor starts and well before advanced cervical dilation has occurred.[11] On the other hand, administration of tocolytics to a woman who is not in labor may unnecessarily expose the woman and her fetus to the risk of adverse side effects. Unnecessary hospital visits can also be costly and psychologically burdensome for a woman who is not truly in labor. For these reasons and because administration of tocolytics usually entails transporting the mother to a clinical setting, accurate prediction and early diagnosis of preterm labor are high priorities in the medical community.

2. Diagnosis of Labor

ACOG defines a uterine contraction as the temporary shortening of uterine muscular fibers, which on relaxation return to their normal length.[12] The mean frequency of contractions tends to rise with increasing gestation, the frequency of contractions increases 24 to 48 hours before the onset of labor (whether at term or preterm), and, at any given gestational age, the mean

11. Dyson DC et al., "Monitoring women at risk for preterm labor," 338 New Eng J. Med. 1998 Jan 1; 338, 15-19.

12. Cunningham, supra. note.

contraction rate of women destined for preterm labor is higher than the mean contraction rate of women destined for term labor.[13] Efforts to predict and detect preterm labor have thus typically focused on accurate assessment of the frequency, duration, and relative intensity of uterine contractions in pregnant women. Uterine contractions in and of themselves are not necessarily indicative of labor. Contractions of the uterus occur throughout pregnancy. [14] Moreover, for a period of time before the onset of true labor, many women experience "false labor" -- also known as "false uterine contractions" or "Braxton Hicks contractions." To distinguish between false and true Labor, a physician may rely on a variety of factors, including whether there has been "show" (discharge of blood and mucus from the vagina), whether the contractions are regular, whether the intensity and duration of the contractions are increasing, whether there is progressive dilation and effacement of the cervix, whether there is discomfort in the back or chiefly in the lower abdomen, and whether sedation is effective.[15] Uterine contractions are only one, albeit probably the most important, of the things a physician may monitor in order to diagnose true labor. Most women presenting to the hospital or physician's office with suspected preterm Labor are immediately put on a uterine contraction monitor and observed for their frequency of occurrence and relative amplitude.

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13. See, e.g., 3/6/99 Tr. at 3 1 (Parisi, MD, expert witness). AU transcript references are to meetings of the Obstetrics and Gynecology Devices Panel (OB/GYN Panel), unless otherwise indicated.

14. Cunningham supra note.

15. Cunningham GF: Williams Obstetrics, 18th Ed. Stanford Connecticut, Appleton & Lange, 1989.

B. Legal Background

1. Classification of Devices

Classification of a medical device turns on the perceived risks of the device and the extent to which various regulatory controls will reduce the risk. Class I devices have the least risk and the fewest controls, Class III the most.

All devices in all classes are subject to the "general controls" in the FD&C Act and corresponding FDA regulations.[16] These include requirements for facility registration and product listing with FDA, adherence to good manufacturing practices, and the maintenance of records and filing of reports regarding marketing experience. Class II devices are also subject to "special controls." The statute contains a non-exhaustive list of "special controls," including performance standards, postmarket surveillance, patient registries, and guidelines (including guidelines for the submission of clinical data).

A Class III device is one that (1) is purported or represented to be "for a use in supporting or sustaining Me" or "for a use which is of substantial importance in preventing impairment of human health"; and (2) for which insufficient information exists to determine that special controls would

16. See 21 U.S.C. 360c(a)(l)(A)

provide reasonable assurance of its safety or effectiveness.[17] A device is also Class III if it "presents a potential unreasonable risk of illness or injury" and the premarket approval process is necessary to provide reasonable assurance of its safety and effectiveness.[18] For a Class III device, the manufacturer must secure premarket approval under Section 5 15, by demonstrating with clinical studies that there is a reasonable assurance of the device's safety and effectiveness.

For a Class II device (and some Class I devices), a manufacturer need only submit to FDA a premarket notification under Section 5 1 O(k). Under this provision, the manufacturer must demonstrate that its device is substantially equivalent to a legally marketed "predicate" device, by showing that it has the same intended use and does not have any different technological characteristics that raise new questions of safety or effectiveness.[19]

2. Reclassification of Devices

FDA may reclassify a device on its own initiative or at the request of a manufacturer.[20] FDA may reclassify a device from Class III to Class II if it determines "that special controls would provide reasonable assurance of the safety and effectiveness of the device and there is sufficient information to establish special controls."[21]

17. Id. 360c (a)(l)(C).
18. Id. 360c (a)(1)(ii)(II).
19. Id. 360c (i).
20 Id. 360c (d), (e), (f).
21. Id 360c(e); 21 C.F.R. 860.130 (c)(l).

In determining the appropriate classification of a device, FDA must consider the following factors: (1) the persons for whose use the device is intended, (2) the conditions of use described in the device labeling, (3) the probable benefit to health weighed against any probable injury or illness from use of the device, and (4) the reliability of the device.[22]

C. Regulatory History of HUAMs

As discussed below, the history of FDA's regulation of HUAMs shows that both FDA and the Obstetrics and Gynecology Devices Panel (OB/GYN Panel) determined that HUAMs, when intended for PTL use, are Class III and reaffied that determination on numerous occasions throughout the 1990s. They also reaffirmed numerous times that a randomized multi-site clinical study of each device is necessary to provide reasonable assurance of its effectiveness when used in the early detection of PTL. Indeed, at least three times since 1995, manufacturers have apparently been unable to generate adequate proof of such effectiveness in clinical studies of their HUAMs.

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22. 2 1 C.F.R. 860.7(b) (1) -(4)

1. Class III Status

On April 3, 1979, following enactment of the Medical Device Amendments of 1976, FDA issued a proposed regulation to classify preamendment uterine activity monitors in Class II.[23] As described in the proposed regulation, the intended use of the device was "to monitor the progress of labor" in clinical settings.[24] The device was finally classified in Class II on February 26, 1980.[25]

FDA later accepted premarket notifications for the use of tocodynamometers to monitor uterine activity at home. For instance, on June 19, 1984, FDA cleared a device manufactured by Advanced Medical Systems, Inc. (AMS) for use in detecting and measuring uterine contractions in either the home or the hospital with any patient, at term or preterm.[26] Later the same year, FDA cleared a similar device manufactured by Tokos, which was intended to "record preterm uterine activity at a site remote from the health care practitioner" and to "monitor[] patients who are identified as at risk for premature birth."[27]

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23. 44 Fed Reg. 19228 (April 3, 1979)

24. Id.

25. 45 Fed. Reg. 12696 (February 26, 1980) 21 C.F.R. 8842720

26. See K840747. In early 1987, Healthdyne entered into an agreement to distrobute the AMS device.

27. See K8430 11.

By the fall of 1985, however, FDA had begun to rethink its treatment of ambulatory uterine activity monitors. The cleared 510(k)s had been submitted not only for general monitoring of uterine activity during pregnancy but also specifically for monitoring of uterine activity during pregnancy in order to determine the potential for preterm delivery. FDA concluded in 1985 that, although these devices had been used for general monitoring prior to 1976, none were used for preterm monitoring.[28] After asking Tokos to submit a 5 1 O(k) for preterm use of its HUAM, FDA found the device "not substantially equivalent" to pre-amendment tocodynamometers, thereby placing the devices -- when intended for PTL use -- in Class III. Claims relating to preterm use would thus require clinical studies and premarket approval applications.

2. Decisions Regarding PMAs

Although the original 5 1 O(k)s were never cancelled, in 1986 monitor manufacturers began to submit premarket approval applications supported with data from clinical studies. As discussed below, seven PMAs were submitted, and three approved. The three approvals came after FDA changed its view (in 1989) of the appropriate clinical endpoint. Even after the first approval, however, one manufacturer's PMA was rejected, and after all three approvals, two other manufacturers apparently failed to generate adequate proof of effectiveness in clinical trials of

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28. See 5/26/88 Tr. at 86 (Pollard, the Executive Secretary of the OB/GYN Panel.

their HUAMs. Throughout this time, both FDA and the OB/GYN Panel, which advises FDA on the approvabihty of HUAMs, have insisted that -- no matter what a manufacturer might claim -- a tocodynamometer is, in fact, intended to detect preterm labor (i.e., not just uterine contractions) and that the manufacturer must show clinical utility in order to provide reasonable assurance of the device's effectiveness.[29]

Tokos' PMA. Tokos submitted its PMA in November 1986, seeking approval of the device as an "aid to physicians in early detection of preterm labor, management of tocolytic therapy, and prolongation of pregnancy." Several clinical studies were presented to the Panel, including a study by Katz in which patients who used a monitor were compared with patients who did not. The proportions of patients who developed preterm labor were similar in the two groups. However, on admission, all monitored patients were suitable candidates for long-term tocolysis, as compared with only 35 percent of the unmonitored patients. Ultimately, 88 percent of the monitored patients, as compared to 59 percent of the controls, delivered at term. A study by Morrison was presented, which compared monitored patients with patients who attempted to detect contractions by palpitation. Both groups had the same prenatal care and educational

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29. See, e.g., Tr. at 140-142 (Wager, OB/GYN Panel, explaining why Healthdyne PMA muat show clinical outcome.)

intervention. Again, the proportions of patients who developed preterm labor were similar in both groups, and again many more patients in the monitored group were suitable for long-term tocolytic treatment when they arrived at the hospital.

The Tokos PMA was presented to the OB/GYN Panel on May 26, 1988. The Panel concluded that: (1) predictions drawn from the strip chart recording of uterine activity using standardized pattern recognition criteria, e.g., contraction frequency over a given period, correlated to a diagnosis of preterm labor; and (2) the total system of nursing management and device monitoring of women at high risk of preterm labor was beneficial.[30] Nevertheless, the Panel recommended against approval of the device and recommended that FDA require the-submission of further clinical data distinguishing the contribution of the device from that of the nursing service.[31]

Healthdyne's First Two PMAs. Healthdyne submitted its first PMA in October 1988, seeking approval for use of the device to detect and record uterine activity at or beyond the 24th week of gestation of a high risk pregnancy, in a non-institutional setting, and to transmit that information to a remote location. The pivotal study presented within the PMA involved over 800 high risk

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30. 5/26/88 Tr. at 149-150, 161-63.

31. 5/26/88 Tr. at 17'1.

participants, over 4000 physician contacts, and 6995 physician interventions. Data from patient contacts and physician interventions were presented within the following categories: (1) contacts and corresponding interventions based exclusively upon uterine contraction information provided by the device; (2) contacts and corresponding interventions based exclusively upon subjective comments provided by the patient to the nurse or treating physician; and (3) contacts and corresponding interventions based upon a combination of those items. The study results confirmed that patient contacts and corresponding physician interventions occurred more frequently for uterine contraction activity detected by the device than for subjective comments.

The OB/GYN Panel reviewed this PMA on March 6, 1989. At the conclusion of the meeting, the Panel recommended against approval of the device. The Panel concluded that, no matter how accurate in detecting and transmitting uterine contractions, the device could not be viewed "in isolation from clinical benefit and outcome consideration."[32] Concerns were raised about isolation of the effect of the device from any contribution by the nurses; additionally Healthdyne failed to show that the increase in intervention due to the HUAM had a positive effect on clinical outcome. The Panel reaffirmed the need for clinical data[33]; one Panel member

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32. 5/6/89 Tr. at 229 (Connell, OB/GYN Panel)

33. See, e.g., 5/6/89 Tr. at 168-69 (Wager, OB/GYN Panel); 5/6/89 Tr. at 214 (Bohon, OB/GYN Panel); See also 5/6/89 Tr. at 212 (Yin FDA) (" I suggest the Panel would definitely look for clinical benefit.")

suggested that ambulatory tocodynamometer manufacturers should show, by a controlled clinical trial, that their devices were more effective in reducing preterm birth than a nursing service that contacts the patients several times a day and elicits signs and symptoms.[34]

Healthdyne submitted a second PMA in April 1990, re-evaluating the study data to determine whether uterine contraction information could be used as an adjunct risk scoring test to identify which high risk patients were likely to deliver prior to term. Clinical utility was measured by comparing the predictive ability of the uterine contraction risk scoring test with the predictive ability of traditional risk scoring systems. A uterine contraction risk scoring test was identified that predicted in a statistically significant manner which high risk women would likely deliver prior to term. However, on June 11, 1990, the OB/GYN Panel reviewed and rejected the second Healthdyne PMA, on the basis of a lack of evidence of clinical utility.

PDS's PMA. Physiological Diagnostic Service (PDS) submitted a PMA in November 1989. PDS was required to submit the results of a clinical study to support the PMA. The pivotal clinical trial was a prospective randomized controlled study. The study examined whether

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34. 5/6/89 Tr. at 140-41 (Wager, OB/GYN Panel)

the device could detect preterm labor earlier, as evidenced by cervical dilation (cm) at the time of the diagnosis of preterm labor. The study involved two groups of women: women who received standard high risk care plus the monitor, and women who received only standard high risk care. Women in the "monitored" group had significantly less cervical dilation at the time of diagnosis than women in the "not monitored" group. The results of this study were published in 1991 .[35]

The OB/GYN Panel discussed this PMA on January 18, 1990, and April 4, 1990, and on September 12, 1990, FDA approved the PDS PMA for one indication (earlier detection of preterm labor) in one patient group (patients with a previous history of preterm delivery).

Healthdyne's Third PMA. In July 1992, Healthdyne submitted its third PMA. Healthdyne was required to submit the results of a clinical study to support its PMA. The study was performed using the same clinical protocol and endpoints as those used by PDS -- women prospectively randomized to a "not monitored" or "monitored" group, and assessment of cervical status as measured by cervical dilation (cm) at the time of the diagnosis of preterm labor. The results were comparable.

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35. See Mou SM et al., "Multicenter randomized clinical trial of home uterine activity monitoring for detection of preterm labor," Am.J. Obstet. Gyecol. 1991; 165:858-66.

The OB/GYN Panel met in September 1994 to discuss the regulatory status of HUAMs, while the Healthdyne PMA was pending, and reaffirmed both the need for clinical data and the endpoint it had chosen earlier.[36] The PMA was approved on September 29, 1995. The results of the underlying study were also published in 1995.[37]

CareLink's PMA. CareLink's PMA for the CareFone(device made the same claim as PDS and Healthdyne -- that the device was indicated for use in conjunction with standard high risk care, for the daily at-home measurement and recording of uterine activity in pregnancies at or beyond 24 weeks of gestation for women with a history of prior preterm delivery, so as to aid in the early detection of preterm labor. CareLink was required to submit the results of a clinical study to support its PMA. The pivotal study was performed using the same clinical protocol and endpoints as used by PDS and by Healthdyne in its third PMA. CareLink found a statistically significant difference between the mean cervical dilation of the monitored group (1.5 cm) and the control group (2.25 cm) at the time of diagnosis of preterm labor. The PMA was approved on

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36. See 9/2/94 Tr. at 205 (vote).

37. See Wapner RJ et., " A randomized multicenter trial assessing a home uterine activity monitoring device used in the absence of daily nursing contact," Am.J. Obstet, Gynecol. 1995;172:1026-34.

September 29, 1995. The results of the underlying study have never been published.

AMS's PMA. American Medical Systems (AMS) submitted a PMA in March 1991, for an HUAM which it claimed would, when used by women with twin gestations in combination with standard high risk care, increase the percentage of women seeking care while favorable for long-term suppression and improve neonatal outcomes. The pivotal study involved 25 1 patients at risk for preterm labor who received an initial educational session about preterm labor, were taught the techniques of self-palpation for uterine activity, and were followed up with weekly cervical exams. Patients were randomized into two groups: one in which the home uterine monitoring tracings were analyzed and the number of contractions reported back to the patient, one in which home uterine monitoring tracings were not analyzed or used. Both the educational program and home uterine monitoring were found to increase the percentage of women with preterm labor who sought care while still favorable for intervention, resulting in a decreased incidence of preterm births and improved outcome. Addition of home uterine monitoring to the educational program was found to significantly improve outcome in twin gestations but not in singleton gestations.[38]

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38. Dyson DC., et al., "Prevention of preterm birth in high risk patients:the role of education and provider contact versus home monitoring, " Am.J. Obstet. Gynecol, 1991; 164: 756-62.

The OB/GYN Panel deemed the device unapprovable in April 1993 on the grounds that the clinical study had an insufficient number of subjects and should not have been limited to one medical center. Both FDA and the Panel reaffirmed the need for clinical data and reaffirmed the endpoint they had previously recommended.[39] Thus, the clinical data for this device were deemed inadequate to show its particular contribution to use for detection of PTL, in contrast to the data supporting the PMA approved for PDS.

Caremark. Caremark sponsored a clinical efficacy study of its "First Activity@" HUAM device, which was discussed at the April 1995 meeting of the OB/GYN Panel. The study showed that uterine activity data obtained from this device, when added to daily nursing contact, was not linked to earlier diagnosis of preterm labor or lower rates of preterm birth or neonatal morbidity.[40] During this meeting, both FDA and the Panel confirmed both the need for clinical data and the study design endpoint they had recommended previously.[41] Caremark, which was primarily in the business of selling preterm labor management services, did not submit a PMA to

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39. See, e.g., 4/30/93 Tr. at 236-37 (Pollard, FDA); 4/30/93 Tr. at 238 (DeJoseph, OB/GYN Panel); See generally 4/30/93 Tr. at 235-71.

40. "The Collaborative Home Uterione Activity Monitoring (CHUMS) Group, "A Multicenter randomized controlled trial of home uterine activity monitoring: Active versus sham devices," Am.J. Obstet. Gynecol. 1995; 173: 1120-27.

41. 64 Fed Reg. at 41437; 4/24/95 Tr. at 135-36 (Williams FDA); 4/24/95 Tr. at 152 (Hill, OB/GYN Panel); 4/24/95 Tr. at 154-55 (Wager, OB/GYN Panel).

support pre-term claims for its device. Again, the clinical data from the study of this particular device contrasts with the data from the clinical studies supporting approval of the PDS, Healthdyne, and CareLink PMAs, which did demonstrate safety and effectiveness.

3. Reclassification Petition

Corometrics Medical Systems has been studying its Model 600 HUAM device for preterm labor under a December 1992 investigational device exemption (IDE).[42] However, Corometrics did not submit data from that study in a PMA. Instead, in August 1997 Corometrics submitted a petition requesting that HUAMs for the early detection of PTL in high risk patients be reclassified from Class III to Class II. In its reclassification petition, Corometrics argues that "new information" -- specifically, clinical data and medical device reporting data -- "has become available to support that general and special controls are sufficient to reasonably assure safe and effective use of the device."[43]

While the petition lists 79 "references," the section entitled "New and/or Valid Scientific Information" makes clear that only 38 of the references are relied upon as scientific information to support the reclassification petition.[44] Moreover, Corometrics concedes that not all of these

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42. "Corometrics Home Uterine Activity Monitor Reclassification Request To Be Reviewed By Panel," The Gray Sheet (September 22, 1997, ay 6. The Model 600 gained 5 10(k) clearance for full term monitoring in late 1990.

43. Corometrics Reclassification Petition at 13.

44. Id at 33-47.

actually support its position: "[t]he only issue that does not appear to have any associated controversy" among the 38 studies, the petition argues, "is the adverse effects of HUAM."[45] In essence, Corometrics argues that FDA should ignore the controversy over effectiveness and downclassify the device because it is indisputably safe based upon the available published literature.

The OB/GYN Panel met in October 1997 to discuss the Corometrics petition. During the meeting, ACOG presented strong opposition to the Corometrics HUAM reclassification petition. Notwithstanding this opposition, Panel members voted to recommend that HUAMs be placed in Class II.. In doing so, however, the Panel raised several questions about the effectiveness of HUAMs and concerns about the impact on mothers and fetuses if the HUAM was not effective, repeatedly expressing a desire for more clinical studies.[46] In July 1999, FDA published a Notice in the Federal Register, proposing to place HUAMs in Class II and requesting public comment on the proposal.[47] FDA identifies five risks to health posed by HUAMs: (1) electric shock and/or injury; (2) skin irritation and sensitization; (3) unnecessary evaluation and treatment; (4) physical disabilities and psychological burdens resulting from the clinical management of woman diagnosed with preterm labor; and (5) risks from use in unproven patient populations.[48] Most of these risks,

45. Id. at 41.

46. See page 58, infra.

47. 64 Fed. Reg. 41435 (July 30, 1999).

48. Id. at 33-47.

FDA writes, are "indirect effects attributable to incorrect monitoring information or misinterpretation of monitoring information leading to misdiagnosis."[49] FDA also states that the "concern that the use of the device would result in an increase in the number of hospital visits and use of tocolytics was not borne out in the published literature."[50] Furthermore, the risk of misdiagnosis "is generally mitigated by proper training, adequate labeling, and limited use of the device by the clinician."[51] Thus, FDA proposes reclassification of HUAMs with two special controls: (1) mandatory patient registries; and (2) a guidance document for submission of 510(k) notifications that would incorporate consensus standards on electrical and material safety, bench testing requirements, clinical validation studies, and labeling requirements to discourage off-label use.

III. ARGUMENT

A. Reclassification of HUAMs as Class II Devices Would Be Unlawful.

Reclassification of HUAMs would be unlawful for three reasons. First, FDA's reclassification decision is unlawful because there is no "new information" to support

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49. Id., at 41438.

50. Id.

51. Id.

reclassification. Second, FDA is relying on clinical data from the PMAs submitted by PDS, Healthdyne, and CareLink, in violation of Section 520(h)(4) of the FD&C Act. Third, FDA's reclassification decision is a complete reversal of agency policy that lacks support in the administrative record.

1. The Corometrics Petition for Reclassification Must Be Denied Because No "New Information" Has Become Available Since The Class III Determination.

The sole basis for Corometrics' petition to reclassify HUAMs from Class III to Class II is that "new information has become available" since FDA imposed Class III designation and PMA requirements.[52] "Based on the new information," Corometrics requests reclassification.[53] Corometrics purports to summarize this "New Information" in its petition.[54]

FDA must deny the Corometrics reclassification petition because neither the petition nor FDA's notice of proposed reclassification demonstrates that there has been any "new information" since FDA's imposition of Class III PMA requirements on HUAMs for early detection of PTL.

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52. Corometrics Reclassification Petition at 8.

53. Id.

54. Id. at 33.

Since 1986, FDA has required PMAs for HUAMs intended for early detection of PTL in high risk patients. FDA determined that a clinical study of each individual product was required to demonstrate its effectiveness in contributing to the early detection of PTL as evidenced by cervical dilation at the time of PTL diagnosis. The OB/GYN Panel reaffirmed this requirement in 1990, 1993, and 1994.[55] At its meeting in April 1995, the OB/GYN Panel reaffirmed both this clinical efficacy study requirement and its recommendations regarding acceptable elements of study design. Two of the three approved PMAs were not approved until September 29, 1995.

The references cited by FDA to support its proposed reclassification decision are not "new" since the Class III status and clinical study requirements were reaffirmed in 1995. Of the 16 references cited by FDA, 8 are OB/GYN Panel Meetings from 1988 through 1995, 5 are literature references dated between 1988 and 1992, and 1 is a literature reference dated 1995.[56] (The other two are the Corometrics petition and the 1997 OB/GYN Panel meeting.)

Likewise, the Corometrics petition fails to contain the necessary "new information" to support the requested reclassification. As to safety, Corometrics relies on voluntary standards that were published before 1995, when FDA and the Panel reaffirmed the Class III status and

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55. See pages, supra.

56. 64 Fed. Reg. at 41439.

clinical study requirements, and many are dated 199 1 or earlier.[57] The petition also relies on the representation that "no MDRs have been reported for HUAM devices."[58] However, even before the petition was filed, some medical device reports had been reported for PTL use of these devices.[59] Neither Corometrics nor FDA mentions the MDRs. Even if the MDR analysis could be considered "new information," however, FDA has failed to make any findings as to whether the favorable MDR history was attributable to the PMA requirements of safety and effectiveness, such that removal of such requirements could adversely affect the history of safe use of HUAMs for detection of PTL in high risk patients.

The petition also lacks the "new information" with respect to clinical efficacy that is required for reclassification. Section 7 of the petition purports to summarize the "New Information" supporting reclassification.[60] It lists 38 "studies that relate to home uterine activity

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57. See Reclassification Petition at 27-30.

58. Id. at 20, 22.

59. We are aware of several, including FDA0033224-1994-02 (transmission Problems), FDA0033224-1994-0001 (fully dilated cervix and emergency Caesarian Section breech presentation within approximately four hours of monitor reading that uterine activity was below baseline), and FDA0033224-1003-0002 (fetal demise). These MDRs were found using the Maude system on the FDA web site. Data were insufficient in each instance to determine whether the device caused or contributed to the event.

60. Reclassification Petition at 33.

monitoring."[61] Of these, 29 predate 1992, and 33 predate 1995, when FDA and the OB/GYN Panel last reaffirmed the Class III status of HUAMs for PTL use. Corometrics cites only five publications dated 1995 or later: Beckmann, Colton, Devoe, and two by Dyson.[62] These studies do not provide "new information" of reasonable assurance of safety and effectiveness sufficient to support reclassification. The Beckmann study concerned only the accuracy of maternal perception of contractions; it showed that women are unable to perceive accurately the presence or absence of preterm uterine activity. The Colton piece is a meta-analysis of other investigators' clinical studies previously available to FDA. The Devoe (CHUMS) piece was presented to the OB/GYN Panel in April 1995. Finally, the two Dyson publications do not support a finding of reasonable

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61. Id. at 33, 34-37.

62. See Beckman CA et al., " Accuracy of maternal perception of preterm uterine activity," Arn.J. Obstet,. Gynecol. 1996, 174(2) : 672-75; The Collaborative Home Uterine Monitoring (CHUMS Group, "A multicenter randomized controlled trial of home uterine activity monitoring: Active versus sham devices," Am J. Obstet. Gynecol. 1995; 173 : 1120-27; Colton T. et al. , " A metaanalysis of home uterine activity monitoring," Am J. Obstet. Gynecol. Nov. 1995, 173 (5): 1449-1505; Dyson DC et al., " A multicenter randomized trial of three levels of surveillance in patients at risk for preterm labor" Am. J. Obstet. Gynecol. 1997: S30; Dyson DC et al., "A multicenter randomized randomized trial of three levels of surveillance in patients at risk for preterm labor -- twin gestation subgroup analysis," Am. J. Obstet. Gynecol. 1997: S118.

assurance of safety or effectiveness. Both Dyson publications refer to one clinical study. The final results of that study were also discussed by the OB/GYN Panel in 1997.[63] and then published in 1998.[64]

Dyson randomly assigned 2422 pregnant women with known risk factors for preterm labor (including 844 women who were pregnant with twins) to receive education and to have either weekly contact with a nurse, daily contact with a nurse, or daily contact with a nurse and home monitoring of uterine activity. The nurses elicited the women's own assessments of their symptoms and signs of preterm labor. The primary endpoint was the incidence of birth at less than 35 weeks of gestation. Secondary endpoints included cervical status at the time preterm labor was diagnosed and birth weight. There were no significant differences among the groups in the incidence of birth at less than 35 weeks, in the mean amount of cervical dilation at the time preterm labor was diagnosed, or in birth weight. Daily contact with a nurse increased the mean number of unscheduled visits to obstetricians and the proportion of women who received prophylactic tocolytic drugs. Dyson concluded that daily nursing contact alone or with a monitor did not improve clinical outcome, and that daily nursing contact with monitoring resulted in

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63. See, e.g., 10/7/97 Tr. at 22-23 (Dr. John Hauth for ACOG)

64. 64. Dyson et al., "Monitoring women at risk for preterm labor." New Eng. J. Med. 1998 Jan 1; 338, 15-19.

increased unscheduled visits and increased non-beneficial use of tocolytics.[65] In short, neither Corometrics nor FDA has cited new clinical data that could plausibly change FDA's view that a PMA under Section 515 is required to assure the safety and effectiveness of HUAMs for PTL in high risk patients.[66] The reclassification petition must therefore be denied.

2. FDA Has Relied on Clinical Data From the Premarket Approval Applications of PDS, Healthdyne, and CareLink, In Violation of Section 520(h)(4) of the FD&C Act.

The only studies that demonstrate the clinical effectiveness of HUAMs, as repeatedly defined by FDA and the OB/GYN Panel, are the three pivotal studies required for approval of the three approved PMAs. The results of two of these studies (Mou and Wapner) were later published; the results of the third study were not. The FD&C Act prohibits FDA from using the safety and efficacy data from the studies contained in these PMAs -- whether or not reports of the

65. FDA appears to have overlooked Dyson's three publications in its July 1999 Notice, as it states that the "concern that the use of the device would result in an increase in the number of hospital visits and use of tocolytics was not borne out in the published literature. Fed. Reg. at 41438. Surprisingly, a Corometrics representative cited this study in support of its petition when speaking to the OB/GYN Panel. 10/7/97 at 44, 47-48 (Maria Fouts, Corometrics).

66. Appendix A contains a comprehensive list of clinical studies on HUAMs known to FDA when it confirmed Class III status in 1995.

studies have been published -- as the basis for reclassification of HUAMs for early detection of PTL.

Section 216 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) amended Section 520(h) of the FD&C Act, 21 U.S.C. § 360j(h), to provide that information contained in a PMA, excluding trade secrets, shall be available six years after the application has been approved, for use by the Secretary in -- among other things -- approving another device, or classifying or reclassifying another device. Put another way, FDA may not use the safety and effectiveness data in a PMA to reclassify a device until six years have passed since approval of the PMA in question. Section 520(h)(4) contains no exception for published information, nor does the legislative history suggest Congress intended such an exception.

Indeed, Section 520(h)(4) recognizes that the results of the clinical studies would be publicly available before FDA is permitted to rely on the data. Section 520(h)(4)(B) refers to the publicly available summary of safety and effectiveness that accompanies a PMA approval. These summaries typically describe the results of the clinical studies supporting PMA approval, including a discussion of the data, and are available to the public shortly after approval. But FDA cannot use these summaries as the basis to reclassify a device or to approve a competitor's device other than pursuant to the six-year provision. Similarly, if the results of a study required for PMA approval are published in the literature, FDA cannot rely on that publication to reclassify a device other than in accordance with the six-year provision.

The cost of obtaining PMA approval for a new device are high for any PMA applicant. Research and development of new medical technologies requires a significant investment of time. and capital. The PMA process can be lengthy, complex, and costly. In the case of home uterine activity monitors, it was particular long and costly, due in large part to FDA's inability to reach a decision about the appropriate clinical endpoints to establish efficacy. The cost to PDS was $1 million dollars; Tokos spent $2 million; Healthdyne $2.5 million; and CareLink $3.5 million. The six-year provision was enacted in 1997 to replace prior efforts to strike a suitable "compromise between device firms interest in maintaining protection of their PMA data, thus maintaining a competitive advantage, and the FDA's interest in having access to PMA data to determine whether reclassification of the device is feasible."[67]

Recognizing the need to encourage innovation, testing and development of new technologies, Congress has for twenty-three years protected the safety and efficacy data required to obtain PMA approval. As amended by FDAMA, the FD&C Act provides an incentive for device manufacturers to innovate by ensuring the proprietary nature of their safety and efficacy data for six years. Device manufacturers count on the ability to recoup part of their investment in post-approval sales. The six-year provision protects the expectations and investments of PMA holders in order to encourage innovation. And it precludes FDA from relying on the Mou study or the Wapner study, which were required and submitted to obtain PMA approval even though

67. S. Rep. No. 513, 101st Cong., 2d Sess. 25 (1997). Congress had originally enacted a complete prohibition on the use of PMA data, and then a rule that data from a PMA could not be used until the fourth device of its kind had been approved

they were later reported in the literature, to support a decision to reclassify HUAMs.[68]

Moreover, FDA cannot rely on the clinical data in the CareLink PMA, which have never been published. Yet the agency is doing just that in its Notice of reclassification. The CareLink PMA is one of only three approved PMAs for PTL use. FDA, however, relies on "a long history of safe use at home" for HUAMs, asserts that "[s]pecific design choices are not expected to affect the risk to the patient," and relies on data showing that HUAMs "provide a benefit to high risk patients by helping to detect PTL at an early stage, as evidenced by cervical dilation, thereby allowing for early management of PTL."[69] These clinical benefits and safety were demonstrated through the clinical efficacy studies required for the three PMAs, including the CareLink PMA, and FDA cannot rely on that PMA data to reclassify HUAMs. At the very least, FDA should have indicated precisely which clinical data support its reclassification decision, and should have demonstrated that it was not unlawfully relying on PMA data. Absent such findings of fact, FDA's Notice is unlawful.FDA's proposed reclassification of HUAMs violates Section 520(h) of the FD&C Act. The reclassification petition must therefore be denied.

3. Reclassification of HUAMs Would Be Unsupported By the Record and Constitute Arbitrary and Capricious Agency Action.

a.) Reclassification of HUAMs Would Be a Dramatic Change in Policy Without Evidentiary Basis or Specific Factual Findings.

68. Even after six years have elapsed since approval of these PMAs, FDA cannot retrospectively apply the six year provision. See Citizen Petition to the Food and Drug Administration Requesting that the agency issue declaratory order stateting that Section 216 of the Food and Drug Administration Moderization Act of 1997 May Not Be Retroactively Applied by FDA (submitted by the Health Industry Manufacturers Association) (August 9, 1999).

69. 64 Fed. Reg. at 41438

FDA's Notice contradicts the position it has consistently taken over the last decade that clinical efficacy studies are required to provide reasonable assurance of safety and effectiveness for HUAMs for PTL, yet there is no new data to support that change in position. FDA has insisted, most recently in 1995, that preterm use of ambulatory tocodynamometers raises questions about efficacy that can only be addressed with full-scale clinical studies. It is difficult to reconcile the fact that FDA approved only three out of seven HUAMs in over a decade, after a protracted battle over proof of clinical utility, with the fact that it now proposes to approve the fourth HUAM on the basis of a 5 1 O(k) notification without a clinical efficacy study. It is similarly hard to reconcile the Notice with the fact that prior PMAs were approved only after additional marketing restrictions were imposed, beyond those automatically placed on Class III devices.[70] Nowhere in its Notice has FDA addressed why these restrictions are no longer necessary.

Equally hard to understand is the agency's draft guidance document for preparation of HUAM 5 10(k)s, which mandates labeling that: "Clinical data from many studies has shown that the HUAM, when coupled with intensive daily nursing contact, does not provide additional information for the early detection of preterm labor." If this is FDA's view, then the agency has no basis for reclassifying HUAMs so as to eliminate the necessity for further clinical studies that address this point.

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70. The Healthdyne and Carelink HUAMs were approved subject to three restrictions: (1) the sale, distribution, and use of the devices is limited to prescription use in accordance with 21 C.F.R. 801.109; (2) their labeling must specify the requirements that apply to the training of practitioners who may use them; and (3) the sale, distribution, and use of the devices is restricted under Section 502(q) and (r) of the FD & C Act which address device labeling and advertising. See Approval Letters for P920038, P910063. The PDS device was approved subject to the first two restrictions, but not the third. See Approval Letter for P890063.

FDA's new view of the adequacy of special controls also represents a dramatic reversal of position. FDA proposes a guidance document for submission of 5 1 0(k)s which would require bench testing, adherence to certain consensus standards, and labeling that describes the capabilities and limitations of the HUAM system FDA had the authority to impose any or all of these special controls as early as 1990. For example, the standards cited as proposed special controls in the Notice -- International Electrotechnical Commission standards 601-l and 601-2 and International Organization for Standardization standard ISO- 10993 -- predate the approval of the Healthdyne and CareLink PMAs.[71] Bench testing, labeling, and a limited clinical validation study to assure readable tracings are not new. FDA does not offer any explanation for its apparent conclusion that these controls were inadequate when it required PMAs for HUAMs but now are adequate in 1999.[72]

To adopt a significant change in substantive agency policy without any new evidence and without specific findings to provide a rational justification for that change -- as FDA proposes to do here -- is the essence of arbitrary and capricious agency action.[73]

b) FDA Has Failed to Address and Resolve Significant Scientific Issues Raised by the Panel.

FDA's proposed reclassification is unlawful under Section 5 13 and is arbitrary and capricious

71. The first editions of the IEC standards 60601-l and 60601-2 date to 1977 and 198 1 respectively. ISO-10993 dates to May 1995.

72. FDA has proposed to require patient registries as a special control for the reclassified device. For comments on the inappropriateness of this requirement, Matria has joined an industry response to FDA, a copy of which is attached in Appendix B to these comments.

7 3 . Cf. Brown & Williamson Tobacco Corp. V. Food and Drug Administration, 153 F.3d 155, 168-71 (4th Cir. 1998), cert. granted, 119 s.ct. 1495 (1999).

because the agency has failed to address and resolve scientific issues raised by members of the OB/GYN Panel considering the reclassification issue.

First, the general recommendation of the Panel flatly contradicts its specific findings. Panel members were asked whether HUAMs are intended for a use which is of "substantial importance in preventing the impairment of human life," which would trigger a higher standard for reclassification. Inexplicably, although FDA asked the Panel to address this question, Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch of CDRH's Office of Device Evaluation, instructed the Panel to answer the question in the negative.[74] Notwithstanding his repeated statements that HUAMs are not intended for a use which is of substantial importance in preventing impairment of human health, Panel members ignored him[75] and voted that HUAMs are.[76] Furthermore, Panel members specifically concluded that HUAMs present a potentially unreasonable risk of illness or injury.[77] Together, these findings support a decision to maintain the device's Class III status. Notwithstanding these findings, the Panel voted to reclassify the device in Class II.[78] FDA fails to address this anomaly in its Notice.

74. See 10/7/97 Tr. at 64-65 (Pollard FDA)

75. See, e.g. 10/7/97 Tr. at 73 (exchange between Pollard and Blanco, OB/GYN Panel).

76. See 10/7/97 Tr. at 75 (vote).

77. 10/7/97 Tr. at 83 (vote).

78. See 10/7/97 Tr. at 163-66 (vote).

Second, a close reading of the final pages of the Panel transcript makes it clear that Panel members voted for Class II reluctantly, and only because they believed an NIH-sponsored study or a mandatory patient registry would be the best or only way to "conduct" the clinical effectiveness studies they believed were necessary.[79] In short, the Panel voted to reclassify even though they concluded that clinical efficacy studies are necessary for HUAMs for PTL use. This is not a lawful recommendation for reclassification under the FD&C Act. FDA relies on the Panel's recommendation in its Notice, without addressing its lack of basis in law.

In sum, FDA's Notice fails to reconcile the OB/GYN Panel's reclassification recommendation with its call for clinical studies to assure the effectiveness of HUAMs for PTL use, and its findings that HUAMs fit the Class III definition because they are of "substantial importance in preventing impairment of human health" and present a potential unreasonable risk of illness or injury. FDA's proposal for reclassification is therefore unlawful under Section 5 13 of the FD&C Act and the Administrative Procedure Act, 5 U.S.C. $552 et seq.

79. See 10/7/97 Tr. at 113 (Blanco, OB/GYN Panel) (reminding participants about safety and effectiveness concerns and pointing out that "it might actually be a much better approach" to require a patient registry so as to "gain a lot more insight" into "outcomes"); 10/7/97 Tr. at 132 (Domecus, industry representative) ([I}t basically sounds like you're asking for a study of the safety and effectiveness of the device."); 10/7/97 Tr. at 150-5 1 (Diamond OB/GYN Panel))I'm not sure holding it in Class III for the purpose of getting those studies is a realistic expectation."); 10/7/97 Tr. at 163 (Hill, OB/GYN Panel) (That's the one area that I feel very unsure, unhappy about, is that we don't have the information that we need.") id. at 165 (Hill) (I reluctantly voted yes.....I would like to see a study done."); 10/7/97 Tr. at 165 (Neumann, OB/GYN Panel) (I still feel there are major concerns that we need to address regarding this device but I think that the FDA and this Panel have certainly exercised it to the extent humanly possible and I think it's time to move on. ")

B. The Proposed Special Controls Are Inadequate and Inappropriate to Address the Safety and Effectiveness Issues Identified By the Panel and FDA.

FDA proposes reclassification of HUAMs with two special controls: mandatory patient registries; and a guidance document that would incorporate consensus standards on electrical and material safety, bench testing requirements, clinical validation studies, and labeling requirements to discourage off-label use. For the reasons set forth in the industry filing on this point,[80] patient registries are inappropriate as a means to ensure safety and effectiveness. The remaining special controls are also inappropriate, as discussed below.

a) Effectiveness Concerns

Every OB/GYN Panel that has examined an HUAM PMA has expressed concern that HUAMs may not, in fact, have a measurable impact on clinical outcome.[81] Even when not meeting to review a particular PMA, the Panel has recommended that FDA should require that cervical dilation at the time of preterm labor diagnosis be the primary clinical endpoint for HUAM clinical trials.[82] Corometrics conceded in its petition that effectiveness has not been definitively proven, despite thirteen years of clinical trials. FDA glosses over the point in its Notice. The only clinical data required under the proposed guidance document for HUAM 5 1 0(k)s are results from a small study of 25 subjects showing that the device produces readable tracings. It defies common sense for FDA to suggest that a limited 25-person clinical validation studies will show

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80. See Appendix B.

81. See, e.g., 5/6/89 Tr. at 201 (Wager, OB/GYN Panel), 211 (Grimes, OB/GYN Panel, 212 (Perlmutter, OB/GYN Panel), 2 13 (Mordock, OB/GYN Panel, nonvoting), 216 (Bohon, OB/GYN Panel).

82. 9/2/94 Tr. at 206 (vote).

effectiveness, when it rejected more than half the PMAs that came before it with far more data for the very same device. In addition, given that several companies have recently been unsuccessful in generating adequate data from clinical studies of their devices to show safety and effectiveness, FDA lacks evidentiary support for its assertion that HUAMs do not "vary substantially from manufacturer to manufacturer in terms of. . . clinical performance."[83]

b) Safety

Panel members repeatedly expressed concern about the safety of HUAMs.[84] For instance, they expressed concern about off-label use of the devices.[85] They expressed concern about the possible. unnecessary initiation of a "cascade of interventions" including bed rest, hospitalization, and medication.[86] Also troubling to the Panel was the possibility of needless exposure to tocolytics and steroids due to detection of clinically meaningless contractions.[87] FDA's Notice identifies five risks to health posed by HUAMs: electric shock and/or injury; skin irritation and sensitization; unnecessary evaluation and treatment; physical disabilities and psychological burdens resulting from the clinical management of woman diagnosed with preterm labor; and risks from use in unproven patient populations.[88] FDA dismisses the bulk of these safety concerns, writing that they are "indirect" effects attributable to "incorrect monitoring information," "misinterpretation of monitoring information," and "misdiagnosis."[89] Moreover, FDA

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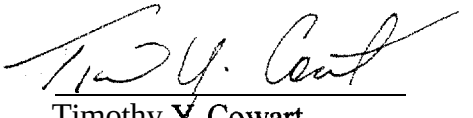
83. 64 Fed. Reg. at 41438.
84. See note, infra.
85. 10/7/97 Tr. at 86-87 (Blanco, OB/GYN Panel); 10/7/97 Tr. at 88-89 (Perlmutter, OB/GYN Panel).
86. 10/7/97 Tr. at 70 (Blanco, OB/GYN Panel) ; 10/7/97 at 78 (Diamond, OB/GYN Panel)
87. See, e.g., 10/7/97 Tr. at 77-78 (Hill, OB/GYN Panel).
88. Id. at 41437-41438.
89. Id. at 41438.

inexplicably asserts that "[t]he concern that the use of the device would result in an increase in the number of hospital visits and use of tocolytics was not borne out in the published literature,"[90] even though the Panel had been considering the same literature on which FDA is relying. (As noted above, FDA overlooked several publications when making this assertion.) FDA's dismissal of safety concerns is puzzling, to say the least. Most importantly, the special controls in question do not purport to (nor could they) address the primary safety issue identified by the October 1997 Panel -- over-prescription of tocolytics.[91] MDRs will not reflect the incidence of this safety problem, because such events likely would be reported as adverse drug events. None of the special controls addresses this concern FDA's dismissal of Panel concerns about unnecessary tocolytic treatment also appears to conflict with the view of the Center for Drug Evaluation and Research that tocolytics raise significant safety issues.[92]

IV. Conclusion

For the reasons explained above, reclassification of HUAMs to "Class II" at this time would be unlawful, inappropriate, and inequitable. Matria therefore urges FDA not to adopt the proposal outlined in the July 1999 Federal Register Notice. Instead, FDA should deny the petition for reclassification.

Respectfully submitted,



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90. 64 Fed. Reg. at 41438

91. Members of prior panels also expressed concern about overtreatment, See, e.g., 9/2/94 Tr. at 141 (Seltzer, OB/GYN Panel).

92. See, e.g., 10/29/92 Tr. of Fertility and Maternal Health Drugs Advisory Committee at 217-218, 239 (votes that committee has concerns about the safety of intravenous ritodrine with respect to mother and fetus, and that oral ritodrine is not effective) ; 5/21/93 Tr. Fertility and Maternal Health Drugs Advisory Committee at 1832 (vote to endorse a limited role for intravenous terbutaline in light of the risks); 4/20/98 Tr. of Advisory Committee for Reproductive Health Drugs at 240-41 (vote to recommend against approval of New Drug Application for atosiban for treatment of preterm labor, on account of concerns about its safety for fetuses.

A

APPENDIX A
CLINICAL STUDIES PRIOR TO SEPTEMBER 1995

In September 1995, when two of the three PMAs were approved, FDA was aware, either by virtue of inclusion in a PMA, discussion at a Panel meeting, or publication in a medical journal, of the following studies on the clinical utility of HUAMs:

* Main and Katz (published 1988). In this study of singleton gestations the predictive value of uterine contraction monitoring in the clinic at least 3 times for 1 hour using a HUAM device. 139 black inner city women were enrolled and the mean contraction frequency during the single hour of testing was greater for the 16 women who developed PTL than for women who delivered at term. Using a contraction frequency threshold of 6 contractions/hour yielded a sensitivity of 75% and a specificity of 79%.

* Katz (published 1986). In this study, presented to the Panel considering Tokos' PMA, 76 patients who used a monitor and were matched for maternal age, parity, and risk factors with 76 who did not use a monitor. The monitored patients recorded uterine contractions for 100 minutes in the morning and 100 minuets in the evening. All patients were instructed to call their physicians if uterine contractions exceeded four contractions per hour. The proportions of patients who developed preterm labor were similar in the two groups. However, on admission, all monitored patients were suitable candidates for long-term tocolysis, as compared with only 35 percent of the unmonitored patients. Ultimately, 88 percent of the monitored patients, as compared to 59 percent of the controls, delivered at term.

* Morrison (published March 1987). The Morrison study, which was presented to the Panel considering Tokos' PMA, compared 34 patients at high risk for preterm delivery who received uterine activity monitoring with 33 similar patients who attempted to detect contractions by palpitation. Both groups had the same prenatal care and educational intervention. The proportions of patients who developed preterm labor were similar in both groups. However, only 45 percent of the unmonitored group were suitable for long-term tocolytic treatment, as compared to 92 percent of the monitored group. The incidence of preterm delivery was significantly reduced among those using the uterine activity device. When short-term neonatal morbidity associated with preterm delivery was compared, adverse effects were found to be significantly lower in the monitored group. The majority of the short-term morbidity in both groups was noted in those delivering preterm, and thus was related to gestational age.

* Nagoette and Freeman (published 1988). In this study of 2,446 women, uterine activity before preterm or term birth was studied. There was a significant increase in the maximum uterine activity from 30 to 44 weeks in all patients. Compared to patients delivering spontaneously at term, average maximum uterine activity was greatest in those delivering preterm. These differences presented for several weeks preceding the onset of spontaneous labor, All pregnancies showed a surge in uterine activity during 3 days before the onset of spontaneous labor.

* Porto (published as an abstract 1987). In this randomized study, patients at risk for PTB were randomized into 3 groups: 1) HUAM, 2)huam WITH RESULTS BLINDED TO CAREGIVERS, AND 3) no HUAM. HUAM use significantly reduced the incidence of PTB and increased the interval of diagnosis of PTL to delivery. HUAM did not appear to lead to overdiagnosis of PTL. The authors stated that the data suggests that while a HUAM program can have a positive effect on PTB prevention, daily telephone contact, coupled with wearing a toco belt 2 hours a day, appears to offer similar benefit in this patientpopulation.

* Iams (published September 1987). 157 women at increased risk for PTB were randomly assigned to receive either HUAM plus frequent nursing contact and education or frequent nursing contact and education only. Comparison of the rate of preterm birth, the incidence of preterm labor and successful tocolysis, and the mean birthweight and gestation age revealed no significant differences and suggested that beneficial effects previously attributed to monitored contraction data may in fact be the result of frequent nursing contact and careful attention to preterm labor symptoms and perceived contractions.

* Iarns (published 1988). This report followed the second year of Iams's study of the Term Guard device. Total study population (both years) was 309 patients. The women were randomly assigned to receive either (a) preterm labor education, frequent telephone contact, and selfpalpation, or (b) preterm labor education, daily telephone contact, and an HUAM. Comparison of preterm labor and preterm delivery rates, mean birth weight, and gestational age at delivery revealed no significant differences between the groups for the second year, nor for the combined data of the two years.

* Sciosca (published 1988). In this study, HUAM was compared to telephone contact with a nurse alone. the authors concluded that there was no measurable impact on the detection of preterm labor. HUAM had no measurable difference in PTB compared to frequent phone contact alone.

* Hill (published 1990). □ This was a prospective randomized multicenter study involving 299 patients at high risk for preterm labor. Patients were assigned to receive either daily home uterine monitoring and nursing contact, or a “standard care” preterm birth prevention program including intensive education and more frequent prenatal visits. Among the monitored patients, there was a significant

increase in early detection of preterm labor (2 cm. or less), successful tocolysis, and prolongation of pregnancy to term. Thirty-one percent of the diagnoses of preterm labor resulted from evaluation of increased uterine activity without associated patient-perceived symptoms.

* Kosasa (published 1990). In this study, 79 patients completed 3,189 days on HUAM. 43 patients experienced preterm labor and benefitted from the HUAM system Earlier detection of preterm labor and better management of oral tocolysis in this group resulted in earlier initiation of maternal tocolytic therapy, which ultimately decreased the preterm birth rate and hospitalization days in the neonatal intensive care unit. Cost analysis of this group demonstrated an savings of $24,000 per patient or an overall savings of $1,032,000.

* Mou (published 1991). In this study, performed to support the PDS PMA, 377 women from three centers, at risk for preterm labor were prospectively randomly assigned to high-risk prenatal care alone ("not monitored") or to the same care with twice-daily home uterine activity monitoring without increased nursing support ("monitored"). The two groups were medically and demographically similar at entry to the study. The primary endpoint of the study was the timing of detection of preterm labor as measured by cervical dilation at the time of diagnosis, Women in the monitored group had significantly less cervical dilation (1.4 cm) than women in the not monitored group (2.5 cm). Mou concluded that "objective assessment of uterine activity, by home uterine activity monitoring in women at high risk for preterm labor, allows detection of preterm labor at less advanced cervical dilation. The clinical importance of this earlier detection of preterm labor is supported by the increased gestational duration after diagnosis of preterm labor and the resultant improved gestational age at delivery, increased birthweight, and decreased neonatal morbidity observed in the monitored group.

* Dyson (published 1991). This study involved 25 1 patients at risk for preterm labor who received an initial educational session about preterm labor, were taught the techniques of se&palpation for uterine activity, and were followed up with weekly cervical exams, All patients were provided monitors. Patients were randomized into two groups: the home uterine monitoring group, in which the home uterine monitoring tracings were analyzed and the number of contractions reported back to the patient, and the education-palpation group, in which home uterine monitoring tracings were not analyzed or used. Both the educational program and home uterine monitoring were found to increase the percentage of women with preterm labor who sought care while still favorable for intervention' resulting in a decreased incidence of preterm births and improved outcome. Addition of home uterine monitoring to the educational program was found to significantly improve outcome in twin gestations but not in singleton gestations. The number of singleton pregnancies was too small to rule out possible benefit from home uterine monitoring in that group.

* Blonde1 (published 1992). This study involved 168 women in four public maternity wards in France who were randomly allocated to two groups: one had a home uterine activity monitor and daily midwife contact, and the other had "standard care" for high-risk women which included home visits by community midwives. The proportion of deliveries before 37 weeks of gestation was slightly higher in the monitored group than in the control group.

* Nagey (published 1993). This study examined the effect of HUAM in women successfully treated for preterm labor. 56 women were randomized to receive HUAM or standard high risk prenatal care. The authors found similar rates of preterm birth in the 2 study groups (57% vs 54%) as well as similar rates of biih before 32 and 34 weeks. The authors concluded HUAM is not effective in reducing the likelihood of preterm delivery in patients successfully treated for preterm labor in current pregnancies.

* CHUMS (published 1995). This study, conducted to support the Caremark PMA, was a randomized controlled double-blinded trial enrolling 1355 pregnant women between 24 and 36 weeks of gestation and at high risk for preterm labor. Each woman was assigned to receive twice daily nursing contact and home uterine activity monitoring, with either active (data revealed) or sham (data concealed) devices. Study endpoints included mean cervical dilation and its mean change from a previous visit at preterm labor diagnosis, change in cervical dilation at preterm labor diagnosis, rates of preterm labor and birth' and neonatal intensive care requirements. The investigators concluded that uterine activity data obtained from HUAMs, when added to daily nursing contact, was not linked to earlier diagnosis of preterm labor or lower rates of preterm birth or neonatal morbidity.

* Wapner (published 1995). This study, conducted to support the third Healthdyne PMA involved 218 women from four centers who were prospectively randomized to routine high-risk prenatal care alone ("not monitored") or to the same prenatal care with twice-daily home uterine activity monitoring without daily nursing support ("monitored"). All women had a history of preterm delivery. The primary study endpoint was cervical status as measured by cervical dilation at the time of the diagnosis of preterm labor. Mean cervical dilation at the time of diagnosis of preterm labor was 1.7 cm in the monitored group and 2.8 cm in the unmonitored group. The median duration of gestation after diagnosis of preterm labor was 2 1 .O days for the monitored group and 3 .O days for the unmonitored group.

* CareLink (presented in the CareLink PMA, which was approved in 1995). The study was performed using the same clinical protocol and endpoints as used by Mou and Wapner. The results showed a statistically significant difference

between the mean cervical dilation of the monitored group (1.5 cm) and the control group (2.25 cm) at the time of diagnosis of preterm labor.

Main DM , Katz M. et al., "Intermittent weekly contraction monitoring to predict preterm labor in low risk women, a blinded study," Obstet. Gynecol. 1988; 72: 757-76 1.

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APPENDIX B

November 23, I999

Dockets Management Branch (HFZ-470)
Food and Drug Administration
5030 Fishers Lane, Room IO6 I
Rockville, Maryland 20850

Dear Sir/Madam:

Matria Healthcare, Inc., Healthy Connections Management Services, Inc., and Secure Care Perinatal Services, Inc., are providing the enclosed industry comments to the Food and Drug Administration (FDA) concerning the July 30, I999, Federal Register announcement proposing that home uterine activity monitors (HUAMs) be reclassified from Class III to Class II.

Our particular focus is to discuss FDA's proposal to impose a requirement to maintain patient registries as a special control, and to present information which demonstrates that patient registries should be withdrawn from the proposal to reclassify HUAM's from Class III to Class II. We believe that patient registries are not an effective or appropriate control, and the imposition of such a requirement would be unduly burdensome on the device manufacturers, distributors, physicians, and patients alike. In addition, the proposed patient registry will not be used to benefit the patient, but its use is clearly designed to restrict, control, and intrude upon the physician's right to use the device based upon the medical needs of the expectant mother.

I. The ability to obtain information about the labor and delivery of the woman and/or information about the nature and type of patient for whom the device was prescribed is well beyond the scope of information that is readily available to the manufacturer and/or distributor.

FDA and the Obstetrics and Gynecology Products Advisory Panel (OB/GYN Panel) apparently misunderstood how HUAMs are used in clinical practice. In general, HUAMs are not legally owned by

the patient, physician, and/or the HUAM manufacturer. In practice, HUAMs are sold by manufacturers to distributors, hospitals, or in some cases physicians, who, in turn, may resell the device to other distributors, hospitals, and/or physicians. Once the device is sold by the manufacturer and/or distributor, the ability of the manufacturer to control the use of the device is limited to promotional practices of the company, combined with the labeling and operating instructions of the device.

Once the device has been sold, other factors influence the ability of the manufacturer to obtain information concerning patient and/or clinical usuage. In particular, the device is often used in different locations with numerous patients over the course of either weeks to days, depending upon the medical condition of the patient. The device can also be prescribed and used by one or more physicians in different locations over the course of weeks to days. As a result the ability to track the device from patient to patient is impossible to perform, since its use can best be described as highly transient. To further complicate the matter, the use and application of the device is highly variable depending upon the physician's assessment of the patient's medical condition. For example, the physician may choose to use the device with the expectant mother until she experiences the onset of labor and subsequent delivery, or the physician may choose to discontinue the use of the device several days or even weeks before the onset of labor and subsequent delivery by the expectant mother. As a result, the existing medical practice precludes and often prohibits the ability to collect and provide the type of information that FDA desires through the use of a patient registry.

2. The use of a patient registry directly intrudes into the practice of medicine.

FDA's proposed rationale for requiring patient registries is that they will provide information on "the patient population for which the device is actually used" and, thus, will help assure the device will

be appropriately used. This rationale is inappropriate in that its intention is to intrude into the practice of medicine.

From a historical perspective, FDA, between 1984 and 1986, allowed manufacturers to obtain a premarket 510(k) notification for the device under 21 CFR 884.2720, external uterine contraction monitor and accessories. At that time, FDA classified the device as Class II, and this classification defined an external uterine contraction monitor as a "device used to monitor the progress of labor". This classification category went on to describe the ability of the device to "measure the duration, frequency, and relative pressure of uterine contractions with a transducer strapped to the maternal abdomen. This generic type of device may include an external pressure transducer, support straps, and other patient and equipment supports." During this time period, manufacturers labeled and promoted their devices accordingly and these devices were used by physicians without limitation to patients gestational age or "term or prior to term" status. In early to mid 1987, FDA became concerned about an expansion of the original intended use claims that were being used by some manufacturers. FDA, in late 1987, made a distinction that the labeled use of HUAM's by manufacturers with patients prior to term was a new use and, as a result, FDA believed that this distinction changed the device classification from Class II to a new Class III category. Although FDA made the distinction between the labeled use of the device with patients at term or prior to term, there was very little effect since FDA had already allowed HUAMs to be used for term and preterm use. Much confusion resulted from FDA's distinction between FDA, manufacturers, and the FDA's OB/GYN Panel. For practical purposes, even though FDA had made a distinction between term and preterm use, physicians have continued to safely and effectively use the device based upon the medical needs of their patients.

It has been a longstanding practice recognized, written about, and publicly acknowledged on numerous occasions by FDA since passage of the Food Drug and Cosmetic Act, that physicians can and routinely do use devices, as well as pharmaceuticals, "off label" to assist them in treating the medical needs of their patients. In accordance with this policy, FDA has focused its regulatory authority by controlling the type and amount of technical and clinical data that is required for obtaining clearances and approvals from FDA, as well as controlling the labeling and promotional practices for devices and pharmaceuticals by manufacturers and distributors. In addition, Congress, through the the FDA Modernization Act of I 997, recognized the need for "off label" use and desired that physicians be allowed access to therapies, devices, and treatments to meet the medical needs of their patients, even though the devices and drugs were approved and labeled for different intended uses. The importance of this principle was emphasized in the recent First Amendment case brought against FDA by the Washington Legal Foundation.

Medical device patient registries are by design generally employed to possess a list of each and every patient(s) who either use or depend upon the medical device to provide ongoing treatment for their medical condition. In most cases, the medical use is associated with long term permanent use of the medical device. It is obvious that the benefit from this form of patient registry is to protect the patient, and to assist the physician, the manufacturer, and the FDA, particularily in the event of a recall or other important safety communication.

In the case of HUAMs, the proposed patient registry is not being used to benefit the patient, the physician, or the manufacturer. Its purpose is to control the use of the device by restricting the physician's ability to use the device based upon the medical needs of the patient. In addition to second

guessing the physician's medical judgement, FDA's action has consequences for third party reimbursement, in that it can result in the denial of insurance coverage for the patient. FDA is taking this action in the absence of data indicating that a problem exists. Since 1984, physicians have safely and effectively used HUAM's to monitor the uterine activity of their patients. This ongoing use of the device by physicians has been based upon managing the medical needs of the patient. while physicians are aware of the labeled indications for use, they likely have used the device in appropriate cases notwithstanding the labeling that distinguishes between term and preterm use, or upon the patient's diagnostic categorization.

3. The patient registry that is being proposed by FDA will not result in information that will be meaningful to either FDA or the manufacturer.

To our knowledge, FDA has never required that a patient registry be required of a monitoring device. FDA has required patient registries involving medical devices involving (a) patients who are receiving ongoing treatment from a medical device, e.g. dialysis, cancer treatments, etc.; or (b) patients who are receiving continuous use from a medical device to treat their medical condition, e.g., heart valve, pacemaker, prosthetic or other implant, etc. The importance of a patient registry for medical implants is easily understood. Also, a patient registry is feasible where a medical device is used exclusively with one patient or the use of the medical device is controlled and exclusive to one patient. In all cases, the patient registry is 100% of the patient population that is utilizing or benefiting from the medical device.

In the present case, FDA is proposing to require some type of structured sample of the use of HUAMs as a means to control use. However, the sample and the method(s) that are being proposed are unclear and not welldefined. In addition, the ability to implement and perfect a patient registry does not take into account several factors which would unduly influence the results. For example, the information that would be provided to FDA would be limited in nature due to the inability to require patients, physicians, and hospitals to release confidential patient information concerning the labor and delivery of expectant mothers to manufacturers and distributors; be narrow and biased in the selection of patients who would comprise the sample, since the time period of use is highly transient with numerous patients using the device during variable time periods; be inaccurate and extremely difficult and expensive to validate due to the lack of consistent relationship between the use of the device and the onset of labor and subsequent delivery of the patient.

4. The expense and resources required to perform a patient registry by manufacturers would be unduly burdensome and excessive.

Should FDA persist in requiring a patient registry for HUAMs, it is projected that each manufacturer and/or distributor would have to dedicate additional staff and employ personnel in order to comply with this new requirement. In total, each manufacturer and/or distributor could spend over $250,000 annually to implement the requirements of the registry. Such requirements involve attempting to obtain permission to access and utilize data from the expectant mother who has no obligation to provide such information; coordinate and obtain pertinent health, device, and outcome information from either the distributor, and/or physician and hospital; analyze and validate the data obtained from the physician and hospital; and prepare documentation for submittal to FDA on a

continuing basis From the proposed use of a patient registry, the derived benefit from its use is not cost effective, is labor intensive, and is unduly burdensome,

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In view of the issues that are presented, we do not believe that the use of patient registries as a special control for HUAMs will be an effective or valid means to identify, describe or characterize the patient population where it is used, nor will it serve to discourage or regulate "off label" use by physicians, an accepted practice in medicine. As a result, we have conclusively demonstrated that the use of a patient registry should be withdrawn from the proposal to reclassify HUAM's from Class III to Class II.

We appreciate the opportunity to provide comments to FDA concerning this recommendation to reclassify HUAMs. If additional information is needed, do not hesitate to contact us.

Sincerely,

Jim Reichmann, President, Womens Health, Matria Healthcare, Inc.

Chip Hunziker, President, Healthy Connections Management Services, Inc.

Teresa Rodewolt, President, Secure Care Perinatal Services

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